

## Non-Nucleoside Reverse Transcriptase Inhibitors

### Glossary of Terms for Supplement

**Carcinogenic:** Producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

**Clastogenic:** Causing disruption of or breakages in chromosomes

**Genotoxic:** Damaging to genetic material such as DNA and chromosomes

**Mutagenic:** Inducing or capable of inducing genetic mutation

**Teratogenic:** Interfering with fetal development and resulting in birth defects

Five non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been approved by the U.S. Food and Drug Administration (FDA): delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Delavirdine is no longer available in the United States and therefore will not be reviewed in this section.

### ***Doravirine (Pifeltro, DOR)***

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There are insufficient human data on the use of doravirine in pregnancy to inform a drug-associated risk determination for birth defects and miscarriage.

#### **Animal Studies**

##### *Carcinogenicity*

Doravirine was not carcinogenic in long-term oral carcinogenicity studies in mice and rats at exposures up to 6 times and 7 times, respectively, the exposure seen in humans who received the recommended dose. A statistically significant incidence of thyroid parafollicular cell adenoma and carcinoma was observed among female rats who received a high dose of doravirine; however, this incidence was similar to the incidence observed among historical controls of the same species. Doravirine was not genotoxic in a battery of *in vitro* or *in vivo* mutagenicity assays.<sup>1</sup>

##### *Reproduction/Fertility*

In rats, doravirine did not affect fertility, reproductive performance, or early embryonic development at exposures (area under the curve [AUC]) that were approximately 7 times the exposure seen in humans who received the recommended dose.<sup>1</sup>

##### *Teratogenicity/Adverse Pregnancy Outcomes*

No adverse embryo-fetal effects were observed in rats and rabbits at doravirine exposures (AUC) that were approximately 9 times (in rats) and 8 times (in rabbits) the exposures seen in humans who received the recommended dose. Similarly, no adverse developmental findings were reported in a prenatal/postnatal study in rats at doravirine exposures that were approximately 9 times the exposure seen in humans who received the recommended dose.<sup>1</sup>

##### *Placental and Breast Milk Passage*

Embryo-fetal studies in rats and rabbits demonstrate placental passage of doravirine. Fetal plasma concentrations observed on gestation day 20 were up to 40% (in rabbits) and 52% (in rats) of maternal concentrations. Doravirine was excreted into the milk of lactating rats at concentrations approximately 1.5 times the maternal concentrations measured 2 hours post-dose on lactation day 14.<sup>1</sup>

#### **Human Studies in Pregnancy**

##### *Pharmacokinetics*

No pharmacokinetic studies of doravirine in pregnant women have been reported.

### *Placental and Breast Milk Passage*

No data are available on placental or breast milk passage of doravirine in humans.

### *Teratogenicity/Adverse Pregnancy Outcomes*

No data are available to inform the risk for birth defects following exposure to doravirine.

### **Excerpt from Table 10<sup>a</sup>**

**Note:** When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of the individual drug components of the FDC during pregnancy.

<b>Generic Name (Abbreviation) Trade Name)</b>	<b>Formulation</b>	<b>Dosing Recommendations</b>	<b>Use in Pregnancy</b>
<b>Doravirine</b> (DOR) <i>Pifeltro</i>  (DOR/3TC/TDF) <i>Delstrigo</i>	<u>DOR (Pifeltro):</u> • 100 mg tablet  <u>DOR/3TC/TDF</u> ( <u>Delstrigo</u> ): • DOR 100 mg plus 3TC 300 mg plus TDF 300 mg tablet	<u>Standard Adult Dose</u> <u>DOR (Pifeltro):</u> • 100 mg once daily with or without food  <u>DOR/3TC/TDF (Delstrigo):</u> • 1 tablet once daily with or without food  <u>PK in Pregnancy:</u> • No PK studies in human pregnancy.  <u>Dosing in Pregnancy:</u> • Insufficient data to make dosing recommendation.  For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, TDF)	No human data are available on placental transfer of DOR, but animal studies suggest that DOR crosses the placenta.  Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in rats or rabbits.

<sup>a</sup> Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

**Key to Acronyms:** 3TC = lamivudine; ARV = antiretroviral; DOR = doravirine; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

## **References**

1. Doravirine [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210806s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210806s0001bl.pdf).